Anti-ischemic agents in addition to dual antiplatelet therapy and full pharmacological treatment for the acute and long-term phases also includes statins, angiotensin-converting enzyme inhibitors (ACEI), and sometimes aldosterone inhibitors in case of low left ventricular ejection fraction or heart failure (1-5).

In this context, bleeding is the most frequent non-ischaemic complication observed in ACS. It has a strong impact on the outcome, with a dose-dependent association between bleeding and risk of death or other ischaemic events. Major bleeding was shown to be associated with a four-fold increase in the risk of death, a five-fold increase in the risk of recurrent MI and a three-fold increase in the risk of stroke at 30 days and long term (6). Minor bleeding can also influence the outcome, albeit to a lesser extent. In addition blood transfusion was shown to have detrimental effects (excess of death and MI, but also lung infections) in many clinical settings, including ACS, PCI, cardiac surgery and acute critical care (7-9).

Prevention of bleeding has become equally as important as the prevention of further ischaemic events. In practical terms, this means that both ischaemic and bleeding risk should be assessed in every single patient. The most efficacious and safest drugs, drug combinations or strategies must be favoured. Priority should be given to drugs and vascular approaches known to reduce the risk of bleeding (3).

This review will address anticoagulant therapy only, with a special focus on fondaparinux, in the light of the most recent developments regarding this drug, e.g. data from FUTURA/OASIS 8 study (11-12).

**Unfractionated Heparin (UFH)**

Historically, UFH was the first anticoagulant to be used in both forms of ACS (with and without ST segment elevation). UFH is a heterogeneous mixture of polysaccharide molecules, with a molecular weight ranging from 2,000–30,000 (but usually 15,000–18,000) Daltons. The therapeutic window is narrow, requiring frequent monitoring of activated partial thromboplastin time (aPTT), with an optimal target of 50–75 seconds, corresponding to 1.5–2.5 times the upper limit of normal. A weight adjusted dose of UFH is recommended, at an initial bolus of 60–70 IU/kg with a maximum of 5,000 IU, followed by an infusion of 12–15 IU/kg/hour, to a maximum of 1,000 IU/hour (13-14).
In NSTE-ACS, a pooled analysis of six trials testing short term UFH vs. placebo or untreated controls showed a 33% risk reduction for death and MI (OR 0.67, 95%CI 0.45–0.99, p=0.04). However, in trials comparing the combination of UFH plus aspirin vs. aspirin alone in NSTE-ACS, a trend towards a benefit was observed in favour of the UFH-aspirin combination, but at the cost of an increased risk of bleeding (15-17). In STEMI, the use of UFH for 48 hours is usually recommended in patients treated with fibrin-specific thrombolytic drugs or undergoing primary PCI (2, 4). In patients treated with non-fibrin-specific thrombolytic drugs, e.g. streptokinase, the use of UFH is less well established. Indeed, in a meta-analysis of trials evaluating UFH as an adjunct to thrombolysis in aspirin-treated STEMI patients, there was no reduction in death/recurrent MI, but an increase in bleeding complications was observed (18). In recent guidelines, UFH in this context is optional.

In the PCI setting, UFH is given as an IV bolus either under activated clotting time (ACT) guidance (ACT in the range of 250–350 seconds or 200–250 seconds, if GPIIb/IIIa receptor inhibitor is given) or in a weight-adjusted manner (usually 70–100 IU/kg or 50–60 IU/kg in combination with GPIIb/IIIa receptor inhibitors) (13). Because of marked variability in UFH bio-availability, ACT-guided dosing is advocated, especially for prolonged procedures when additional dosing may be required. Continued heparinisation after completion of the procedure, either preceding or following arterial sheath removal, is not recommended.

Low molecular weight heparins (LMWH)

LMWHs represent a class of heparin-derived compounds with molecular weights ranging from 2,000 to 10,000 Daltons. They have balanced anti Xa and anti IIa activity, depending on the molecular weight of the molecule, with greater anti IIa activity with increasing molecular weight. LMWHs have several advantages over UFH, particularly an almost complete absorption after subcutaneous administration, less protein binding, less platelet activation, and, therefore, a more predictable dose-effect relationship (13-14). Furthermore, there is a lower risk of heparin-induced thrombocytopenia with LMWHs as compared to UFH. Most LMWHs are contraindicated in case of renal failure with creatinine clearance (CrCl) <30 ml/min. However, enoxaparin dose adaptation is advocated in patients with lower than 30 ml/min CrCl (1 mg/kg once instead of twice daily).

Several meta-analyses have compared the respective efficacy and safety of LMWHs vs. UFH, and particularly, enoxaparin, the most widely prescribed LMWH vs. UFH. Overall, these meta-analyses have shown a trend towards superior efficacy with LMWH/enoxaparin, but at the cost of a non-significant increase in risk of bleeding in NSTE-ACS (15, 19). Notably, the only trial to test enoxaparin vs. UFH using a contemporary approach, with a high rate of PCI, revascularisation, stent implantation and active antiplatelet therapy with aspirin, clopidogrel and GPIIb/IIIa was the SYNERGY trial (20). This trial included 10,027 high-risk patients undergoing early invasive evaluation plus revascularisation, of whom 76% received anticoagulants pre-randomisation. No significant difference was observed in terms of death and MI at 30 days, but more bleeding occurred with enoxaparin, with a statistically significant increase in TIMI major bleeding (9.1% vs. 7.6%, P=0.008) but non-significant excess in GUSTO severe bleeding (2.7% vs. 2.2%, P=0.08) and transfusions (17.0% vs. 16.0%, P=0.16). In retrospect, the excess of bleeding was probably due to a high rate of pre-randomisation use of anticoagulants, and also possibly to frequent post-randomisation cross-over from one anticoagulant to the other. In fact, after adjustment using several modelling techniques, only a modest impact of post-randomisation crossover on treatment effects, including bleeding, was observed (21).

In STEMI, LMWH reduced the risk of death and MI, compared to UFH, but at the expense of an increased bleeding risk (18, 22-23). These data were confirmed in the EXTRACT-TIMI 25 study, where the use of enoxaparin compared to UFH led to a significant risk reduction for death and MI at 30 days, at the cost of a significant increase in the risk for major and fatal bleeding (22). In STEMI patients not submitted to reperfusion therapy, LMWH was shown to improve prognosis, but at the cost of a higher risk of bleeding, particularly intra-cranial bleeds (23).

LMWHs, primarily enoxaparin, are commonly used in the PCI setting in spite of the fact that anticoagulation cannot be easily monitored. In NSTE-ACS patients pretreated with enoxaparin, no additional enoxaparin is recommended during PCI if the last subcutaneous enoxaparin injection was administered less than 8 hours before PCI, whereas an additional 0.3 mg/kg IV bolus is recommended if the last subcutaneous enoxaparin injection was administered more than 8 hours before PCI (13-14). In STEMI patients, there is a paucity of data on this point. The ATOLL study of about 1,000 patients undergoing primary PCI, showed better efficacy than UFH for protecting against further ischaemic events, death and MI complications, without any excess of bleeding (unpublished data).

Direct Thrombin Inhibitors (Bivalirudin)

Bivalirudin binds directly to thrombin (Factor IIa) and thereby inhibits the thrombin-induced conversion of fibrinogen to fibrin. It inactivates fibrin-bound, as well as fluid-phase thrombin. As it does not bind to plasma proteins, the anticoagulant effect is more predictable. Unlike heparin, bivalirudin does not interact with PF4 and it is eliminated by the renal route. Coagulation tests (aPTT, ACT) correlate well with plasma concentrations. These two tests can, therefore, be used to monitor the anticoagulant activity of bivalirudin.

Bivalirudin was tested in the setting of elective PCI, where it showed efficacy as compared to UFH plus GPIIb/IIIa inhibitors, but with a significant risk reduction for major bleeding complications (2.4% vs. 4.1%, P<0.001, for bivalirudin vs. UFH plus GPIIb/IIIa inhibitors). No significant difference was observed in the hard endpoints at one month, 6 months and 1 year (24).

Bivalirudin was tested in the ACUITY study in the setting of NSTE-ACS (25). Bivalirudin plus provisional GPIIb/IIIa inhibitor showed similar efficacy to heparin/LMWHs plus systematic GPIIb/IIIa inhibitors in moderate- to high-risk patients planned for invasive strategy, while significantly lowering the risk of major haemorrhagic complications (25). However, no significant difference in short- and long-term outcomes were observed in ACUITY between these two anticoagulation strategies.
In the setting of STEMI, bivalirudin was tested in the Horizons study (26). In this trial, there was no significant difference in the composite ischaemic outcome at 30 days, but a highly significant risk reduction for major bleeding with bivalirudin plus provisional GpIIb/IIa inhibitors compared to UFH plus GpIIb/IIa inhibitors was observed. At 1 month, there was a significant risk reduction for death, despite an excess of ischaemic events during the first week of evolution, and this reduction was maintained at 1 year. It is thought that in this trial, the reduction in bleeding directly impacted on the risk of death (26).

**Fondaparinux**

The only selective factor-Xa inhibitor available for clinical use is fondaparinux, a pentasaccharide structurally similar to the antithrombin-binding sequence common to all forms of heparin. It inhibits coagulation factor Xa by binding reversibly and non-covalently to antithrombin, with a high affinity. It catalyses antithrombin-mediated inhibition of factor Xa, thereby preventing thrombin generation. Fondaparinux increases 300-fold the ability of antithrombin to inhibit factor Xa. The inhibition of 1 U of factor Xa prevents the production of 50 U of thrombin.

Fondaparinux has a 100% bioavailability after subcutaneous injection with an elimination half-life of 17 hours and can, therefore, be given once daily. It is eliminated mainly by the renal route. It is contraindicated if creatinine clearance (CrCl) is lower than 20 ml/min. It is insensitive to inactivation by platelet-released heparin neutralisation proteins. No case of heparin-induced thrombocytopenia (HIT) has been reported with this drug, even after extensive use in the setting of prevention and treatment of VTE. As a result, monitoring of the platelet count is not necessary. In addition, no dose adjustment and no monitoring of anti-Xa activity are required. Fondaparinux has no significant influence on the usual variables monitored to guide therapy (i.e. aPTT, prothrombin and thrombin times).

The phase II PENTUA study was a randomised, multicentre, double-blind, dose-ranging study that assessed the efficacy and safety of fondaparinux in patients with NSTE-ACS (27). Four subcutaneous doses of fondaparinux (2.5, 4, 8 and 12 mg once daily) were compared with enoxaparin (1 mg/kg twice daily administered subcutaneously). The incidence of the primary efficacy outcome (death, MI and episodes of recurrent ischaemia at day 9) was comparable in the fondaparinux group (37.0% vs. 40.2%, respectively). Bleeding rates in the two study groups were also similar. However, as the lowest dose of fondaparinux (2.5 mg once daily) was significantly more effective (P<0.05) than enoxaparin (30.0% vs. 40.2%), this dose was selected for the phase III OASIS-5 and OASIS-6 trials.

In the OASIS-5 study, 20,078 patients with NSTE-ACS were randomised to receive 2.5 mg subcutaneous fondaparinux once daily, vs. subcutaneous enoxaparin 1 mg/kg twice daily for 8 days maximum (average 5.2 vs 5.4 days, respectively) (28). The primary efficacy outcome of death, MI or refractory ischaemia at 9 days was 5.7% vs 5.8% for enoxaparin vs. fondaparinux respectively (HR 1.01, 95% CI 0.90–1.13), fulfilling the criteria for non-inferiority. At the same time, major bleeds were halved with fondaparinux compared to enoxaparin (2.2% vs. 4.1%, respectively, HR 0.52, 95% CI 0.44–0.61, P<0.001).

Major bleeding was an independent predictor of long-term mortality, which was significantly reduced with fondaparinux at 30 days (2.9% vs. 3.5%, HR 0.83, 95% CI 0.71–0.97, P=0.02), and at 6 months (5.8% vs. 6.5%, HR 0.89, 95% CI 0.80–1.00, P=0.05). At 6 months the composite endpoint of death, MI or stroke was significantly lower with fondaparinux vs. enoxaparin (11.3% vs. 12.5%, HR 0.89, 95% CI 0.82–0.97, P=0.007). In the population submitted to PCI, a significantly lower rate of major bleeding complications (including access site complications) was observed at 9 days in the fondaparinux group vs. enoxaparin, 2.4% vs. 5.1%, respectively (HR 0.46, 95% CI 0.35–0.61, P<0.001) (29).

Interestingly, the rate of major bleeding was not influenced by the timing of intervention after injection of the last dose of fondaparinux (1.6% vs. 1.3% vs 6 hours respectively). Catheter thrombus was observed more frequently with fondaparinux (0.9%) than with enoxaparin (0.4%), but was abolished by injection of an empirically determined bolus of UFH at the time of PCI. As the rate of ischaemic events was similar in both the fondaparinux and heparin groups at 9 days, the net clinical benefit of death, MI, stroke and major bleeding favoured fondaparinux vs. enoxaparin (8.2% vs. 10.4%, HR 0.78, 95% CI 0.67–0.93, P=0.004) (28).

The OASIS-6 study was a phase III, multicentre, randomised, double-blind study of fondaparinux vs. standard therapy (placebo or UFH) in patients with confirmed STEMI (30). Patients were eligible, regardless of their therapeutic management, i.e. thrombolysis, primary PCI or no reperfusion therapy. As in OASIS-5, fondaparinux was administered 2.5 mg subcutaneously once daily; however, the first dose was administered intravenously in order to ensure rapid delivery. Randomisation was stratified by the patient’s indication for the use of UFH, based on the investigator’s judgment. Patients with no indication for UFH were enrolled in stratum 1; they were assigned to receive either fondaparinux or matching placebo for up to 8 days or hospital discharge if earlier.

Patients with an indication for UFH (i.e. patients in whom use of a fibrin-specific thrombolytic drug was envisaged, patients not eligible for thrombolysis but eligible for anticoagulants and patients scheduled for primary PCI) were enrolled in stratum 2. In stratum 2, patients received either fondaparinux up to 8 days or hospital discharge (whichever came first) or UFH for up to 48 hours. The dosage regimen of UFH was an intravenous dose of 60 U/kg followed by an infusion of 12 U/kg/hr for 24–48 hours adjusted to maintain aPTT within the therapeutic range of 1.5 to 2.0 times control. Follow-up was for a minimum of 90 days up to a maximum of 180 days.

A total of 12,092 patients were randomised for treatment. The occurrence of the primary efficacy outcome (composite of death or recurrent MI up to day 30) was significantly (P=0.008) reduced by 14% in patients randomised to fondaparinux. This benefit emerged at day 9 and persisted up to six months after the event. It was consistent according to gender, age, time from symptom onset to randomisation, use of pre-randomisation UFH and type of thrombolytic agent used. Similarly, there was a significant reduction in mortality of 13% at 9 days (P=0.04), 13% at 30 days (P=0.03), and 12% at study-end (P=0.03) in the fondaparinux group vs. UFH/placebo. A trend (P=0.13) towards fewer severe bleeds was evident in the fondaparinux group (1.0%) compared with the control group (1.3%). Throughout the study period, the net clinical benefit, defined by the composite of death, recurrent MI, or severe bleeding, was in favour of fondaparinux.
The effect of fondaparinux on the composite outcome of death or recurrent MI was not statistically different between the two strata, but was more marked in stratum 1 than in stratum 2. Patients who did not undergo primary PCI had a significant risk reduction for death (21% risk reduction, $P=0.03$) and death/recurrent MI (23% risk reduction, $P=0.008$) at six months. Those patients who were not submitted to reperfusion derived a large benefit from fondaparinux, with a trend towards less frequent severe bleeding (1.6% vs. 1.8%, $P=0.06$).

Patients who underwent thrombolysis also derived benefit from fondaparinux as compared to the comparator. Furthermore, within this subgroup, there was no heterogeneity in the response for patients submitted to non-fibrin specific vs. fibrin-specific thrombolytic agents. Lastly, patients submitted to primary PCI did not derive any benefit, with a significant interaction across the groups by type of reperfusion [12].

Fondaparinux was also tested in the setting of elective or urgent PCI at doses of 2.5 mg and 5 mg, given intravenously in the ASPIRE study. This was a multicentre, randomised, blinded, dose-ranging study designed to compare fondaparinux (2.5 mg or 5.0 mg) and UFH, both administered intravenously, in 350 patients scheduled for primary or elective PCI [31].

The incidence of the efficacy outcome (composite outcome of all-cause death, myocardial (re)infarction, urgent revascularisation and the need for bail-out GPIIb/IIIa inhibitors) was 6.0% in the combined fondaparinux group and 6.0% in the UFH group. The incidence of total (major and minor) bleeding occurring within 48 hours after randomisation was 6.4% in the combined fondaparinux group and 7.7% in the UFH group ($P=0.61$). Total bleeding, however, was less common in the 2.5 mg fondaparinux group than in the 5.0 mg fondaparinux group (3.4% vs. 9.6%, $P=0.06$). Abrupt vessel closure and unexpected angiographic thrombus tended to occur more frequently in the two fondaparinux groups as compared to UFH (2.5% and 5.1% for the 2.5 mg fondaparinux dose, 0 and 4.3% for the 5.0 mg fondaparinux dose, vs. 0.9% and 0.9% for the UFH control group [31]).

A total of 6,239 patients (31.1%) enrolled in OASIS-5 underwent PCI during the first 8 days after randomisation (29). Consistent with the data obtained in the overall population, efficacy was similar between the two treatment groups. Furthermore, the bleeding advantage of fondaparinux over enoxaparin in the overall population was maintained, with a significant 55% lower rate of bleeding at day 9 between treatment groups. In patients undergoing PCI within six hours of the last subcutaneous dose of study treatment and who would not have received UFH/placebo per protocol, the rate of major bleeding was also lower in the fondaparinux group (1.6% vs. 3.8%, $P<0.001$).

Vascular access site complications were less frequent ($P<0.001$) in fondaparinux-treated patients. In contrast, catheter thrombosis was more frequent ($P=0.001$) with fondaparinux (0.9%) than with enoxaparin (0.4%). However, adding a single bolus of UFH at the time of PCI made it possible to abolish catheter thrombosis. The average dose of UFH was 47 IU/kg. Of note, major bleeding was significantly ($P<0.001$) lower with fondaparinux irrespective of the use of UFH before PCI. Overall, the net clinical benefit was significantly in favour of fondaparinux.

Patients scheduled for primary PCI in OASIS-6 received single-bolus injections (either fondaparinux or UFH) immediately before the procedure. The dose depended on the pre-randomisation use of UFH and GPIIb/IIIa inhibitors. For patients who required non-primary PCI while still receiving the study drug, an open-label dose of UFH was added at the time of PCI.

A total of 3,788 patients (31.3%) underwent primary PCI during hospitalisation [30]. Efficacy and safety data were similar between the two groups. There was, however, a higher rate of catheter thromboses (0 vs. 22, $P<0.001$) and more frequent coronary complications (225 vs. 270, $P=0.04$) in fondaparinux-treated patients. Again, when open-label UFH was administered prior to PCI, no significant difference in catheter thrombus was observed. The use of additional UFH in fondaparinux patients was well tolerated with similar severe bleeding rates.

The messages that can be derived from the OASIS-5 and OASIS-6 trials are similar. There was no excess of major bleeding in either trial, but a highly significant 48% risk reduction for bleeding in OASIS-5, and a non-significant 23% risk reduction for bleeding in OASIS-6. These results are strikingly different from that observed with enoxaparin which was associated with an excess of bleeding in both OASIS-5 vs. fondaparinux and in EXTRACT-TIMI 25 vs. UFH [22]. In both OASIS-5 and OASIS-6, a significant risk reduction for death, death/MI and death/MI/stroke was observed at 30 days and 6 months. In OASIS-6, the significant risk reduction for death was observed as early as 9 days after randomisation. In OASIS-5, the treatment effect was consistent in all subgroups of patients, including those undergoing PCI, elderly patients and those with renal failure, irrespective of the initial risk category.

In OASIS-6, the treatment benefit was observed mainly in patients not submitted to any form of reperfusion, or in patients submitted to thrombolytic therapy. The excess of catheter thrombosis observed during PCI did not influence outcome in OASIS-5, but resulted in more ischaemic events in primary PCI patients in OASIS-6. This excess of catheter thrombosis in both trials has probably been over-emphasised, and presented as a major drawback of fondaparinux. However, catheter thrombus was observed only in the setting of PCI, and can be prevented by adding a single IV bolus of UFH at the time of PCI.

Last, but not least, in OASIS-5, the risk reduction for bleeding impacted on the risk of death. This was the first time ever that a reduction in bleeding leading to a reduction in death was observed in a clinical trial. The loop is, therefore, closed: an excess of bleeding leads to an increased risk of death, but a reduction in bleeding leads to a reduction in death rate. This is a paradigm shift in the management of ACS.

A mechanistic explanation for the difference between the fondaparinux and enoxaparin regimens has been proposed [32]. Fondaparinux at a dose of 2.5 mg daily leads to ~50% lower anti-coagulant effect as compared with enoxaparin at standard dose, as assessed by anti-Xa activity. Similarly, thrombin generation inhibition is also twice as low with fondaparinux, as assessed by thrombin generation potential. This suggests that a low level of anticoagulation is sufficient to prevent further ischaemic events during the acute phase of NSTE-ACS in patients with full antiplatelet therapy, including aspirin and clopidogrel, plus GPIIb/IIIa inhibitors in many, since there was no difference in primary endpoint between fondaparinux and enoxaparin groups at 9 days in OASIS-5.
This low level of anticoagulation explains the significant reduction in the risk of bleeding. Such a low level of anticoagulation, however, is not sufficient to prevent catheter thrombosis during PCI in a highly thrombogenic environment. This also confirms that an additional bolus of UFH is needed at the time of PCI in patients initially treated with fondaparinux.

The optimal dose of UFH to be administered as a bolus during PCI in patients initially treated with fondaparinux was investigated in the FUTURA/OASIS 8 trial[11]. In this study, 2,026 patients initially treated with fondaparinux, submitted to PCI within 72 hours following initiation of therapy, received either a low-dose IV bolus of UFH (50 IU/kg), regardless of the dose of GPlIb/IIa inhibitors (if any), or standard dose UFH, namely 85 IU/kg (reduced to 60 U/kg in case of use of GPlIb/IIa inhibitors), adjusted by blinded activated clotting time (ACT). PCI was carried out early after the last dose of fondaparinux (4 hours). There was no significant difference between the two groups in terms of the primary composite endpoint (major bleeding, minor bleeding or major vascular access site complications) at 48 hours after PCI (4.7% vs. 5.8%, low vs. standard-dose group (OR 0.80; 95% CI 0.54–1.19; P=0.27).

The rate of major bleeding was not significantly different between the two groups (1.2% vs. 1.4% for the standard vs. low dose groups, respectively), and was similar to that observed in patients submitted to PCI in the fondaparinux arm of the OASIS 5 trial (1.5 % at 48 hours, with the same bleeding definition). Minor bleeding events were less frequent in the low dose group (0.7% vs. 1.7%, low vs. standard dose, respectively, OR, 0.40; 95% CI, 0.16–0.97; P=0.04). The net clinical benefit (major bleeding at 48 hours or target vessel revascularisation at 30 days) favoured the standard dose group (5.8% vs. 3.9% for low vs. standard dose group, respectively, OR, 1.51; 95% CI, 1.00–2.28; P=0.05). The secondary endpoint of death, MI or target vessel revascularisation also favoured the standard dose group (OR 0.80; 95% CI 0.54–1.19; P=0.27).

CONCLUSIONS

In the setting of ACS, four anticoagulants with proven efficacy are currently available. For two of these, namely UFH and LMWH/enoxaparin, the risk reduction for ischaemic events is achieved at the cost of an excess of bleeding. Bivalirudin with provisional GPlIb/IIa inhibitors was shown to be superior to conventional anticoagulation plus GPlIb/IIa inhibitors, by means of a considerable risk reduction for bleeding that impacted on the risk of death in primary PCI patients. Bivalirudin can be administered in patients with or without ST segment elevation who proceed to PCI, but cannot be administered as medical therapy in a conservative treatment strategy. In this context, fondaparinux has been shown in a cohort of more than 32,000 patients to significantly reduce the risk of bleeding, and also to significantly reduce the risk of death, death/MI and death/MI/stroke[33]. Fondaparinux can be administered as first-line therapy, irrespective of the treatment strategy (invasive vs. conservative). The problem of catheter thrombosis is overcome by adding a single bolus of UFH at the time of PCI. This strategy was shown, in the FUTURA/OASIS-8 study, to preserve the benefit of fondaparinux therapy without altering safety[11].


